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Dynamics of H3K27me3 methylation and demethylation in plant development

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Epigenetic regulation controls multiple aspects of the plant development. The N-terminal tail of histone can be differently modified to regulate various chromatin activities. One of them, the trimethylation of histone H3 lysine 27 (H3K27me3) confers a repressive chromatin state with gene silencing. H3K27me3 is dynamically deposited and removed throughout development. While components of the H3K27me3 writer, Polycomb repressive complex 2 (PRC2), have been reported for almost 2 decades, it is only recently that JUMONJI (JMJ) proteins are reported as H3K27me3 demethylases, affirming the dynamic nature of histone modifications. This review highlights recent progress in plant epigenetic research, focusing on the H3K27me3 demethylases.

Histone Methylation and Demethylation

The basic subunit of a chromatin is the nucleosome, which consists of DNA wrapped around the core histone octamer (2 molcules of each of the histone H2A, H2B, H3, and H4). The amino (N)-terminal tails of these histone proteins protrude out of the nucleosome unit and are subjected to extensive post-translational modifications, including but not limited to methylation, acetylation, phosphorylation, and ubiquitination. Some of the histone modifications (e.g. acetylation, phosphorylation) are proposed to function in changing the overall charge of the histone, thereby controlling the degree of condensation of the chromatin fiber.[1] However, more evidences are suggesting that histone modifications (e.g., methylation, acetylation) may serve as binding platforms to recruit other protein complexes onto the chromatin.[2] The histone code hypothesis propose that these histone marks may work in a sequential or cooperative manner to regulate downstream gene activities.[1]

Histone methylation is one of the better-studied histone modifications, which generally occur on the lysine (K) and arginine (R) residues on the N-terminal histone tails. Depending on the location of the amino acid residue and its degree of methylation, it can confer an activating or repressing chromatin status.[2] This histone modification on lysine residues is mainly catalyzed by histone methyltransferases (HMTases) containing the SET (for Suppressor of variegation 3–9, Enhancer of zeste, and Trithorax) domain. In Arabidopsis there are 37 of these HMTases which could add 1, 2 or 3 methyl group to a lysine residue, serving as 'writer' proteins.[3] Located at the globular domain of histone H3, the surface-exposed H3K79 residue can also be methylated by the Dot1 family of methyltransferases, a class of non-SET domain-containing HMTases.[4] However, the Arabidopsis genome has no apparent H3K79 methylation enrichment and does not contain Dot1-like homolog, and it has been suggested that the H3K36me3 marks in Arabidopsis may assume the similar role of H3K79me3 as a transcription elongation mark in animals.[5] Besides the lysine-specific HMTases, the Arabidopsis genome contains another small family of S-adenosylmethionine (SAM) binding-domain proteins that catalyzes the methylation on arginine residues, collectively known as the Protein Arginine Methyltransferases (PRMTs).[6] The PRMTs can catalyze the monomethylation, asymmetric dimethylation or symmetric dimethylation of arginine of histone H3 and H4.

Antagonizing the effect of the HMTases are the histone demethylases, which function as 'eraser' proteins of these histone codes. Unlike acetylation, which dynamism had been shown through the discovery of histone acetyltransferases and deacetylases, histone methylation was previously thought to be irreversible due to the lack of histone demethylases. The human Peptidyl arginine deiminase 4 (PADI4) was the first enzyme shown to be able to antagonize histone arginine methylation.[7,8] However, there are arguments whether to consider PADI4 a histone demethylase because it catalyzes the conversion of methyl-arginine to citrulline instead of an unmodified arginine. A protein-protein BLAST search suggests that the Arabidopsis genome contains no PADI homolog. The existence of other proteins to carry out a similar enzymatic citrullination reaction is uncertain.

The dynamics of histone methylation was finally rectified when the demethylation of lysine 4 of histone H3 (H3K4) was first demonstrated by human Lysine specific demethylase 1 (LSD1) in Hela cells.[9] In Arabidopsis, there are 4 LSD1 homologues, and like the human LSD1, some of them can demethylate modified mono-/dimethylated H3K4.[10,11] Another class of histone demethylase, the JUMONJI (JMJ) proteins, can target all mono-/di-/trimethylated (me1/me2/me3) lysine residues.

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There are 21 JMJ histone demethylases in Arabidopsis which can be categorised into 5 groups based on their overall domain architectures and the similarities of the JmjC domain sequences (**Table 1**). These groups are named KDM5/JARID1, KDM4/JHDM3/JMJD2, KDM3/JHDM2, JMJD6, and JmjC domain-only groups.[12,13] In this review, we focused on recent publications on the Arabidopsis H3K27me3 demethylases from two groups of JMJ proteins, namely the KDM4/JHDM3/JMJD2 and JmjC domain-only group, after briefing on H3K27me3 deposition and Polycomb group (PcG) activities (**Fig. 1**).

Actions of PRC1 and PRC2 on Gene Repression

The H3K27me3 histone modification is correlated with gene repression and is deposited by the PcG proteins.[2] In the Arabidopsis genome, at least 25% of the genes are targeted by H3K27me3 in seedlings, and these epigenetic marks are dynamically regulated during the plant's growth and development.[5,14,15] The PcG proteins were first described in Drosophila and 2 of the most well-characterized PcG complexes are polycomb repressive complex 1 (PRC1) and PRC2. The Drosophila PRC2 complex contains 4 main components (Extra sex comb (Esc), Enhancer of zeste (E(z)), Suppressor of zeste 12 (Su(z)12), and p55) and catalyzes the trimethylation of H3K27 via the catalytic E(z) HMTase.[16] In addition, the Drosophila PRC1 complex, which consists of main subunits Polycomb (Pc), Polyhomeotic (Ph), and the Ring finger proteins Posterior sex comb (Psc) and dRING/Sex combs extra (Sce), catalyzes the monoubiquitination of lysine 119 of histone H2A (H2AK119ub/H2Aub) through the RING ubiquitin ligase.[16]

In animals, the prevailing hierarchical model of PcG action has been well accepted, in which the PRC2 is recruited by the *cis*-acting Polycomb response elements (PREs) and deposits the H3K27me3 mark onto specific location to establish the repressive chromatin state (**Fig. 1**).[16] PRC1 is then recruited to the region due to the specificity of its chromodomain (of Pc subunit) toward H3K27me3 to monoubiquitinate H2AK119 and further reinforces the stable repressive status.[16] However, recent findings revealed that H3K27me3 is dispensable for PRC1 recruitment at Drosophila PREs.[17] Moreover, there are genes targeted by H3K27me3 but lack

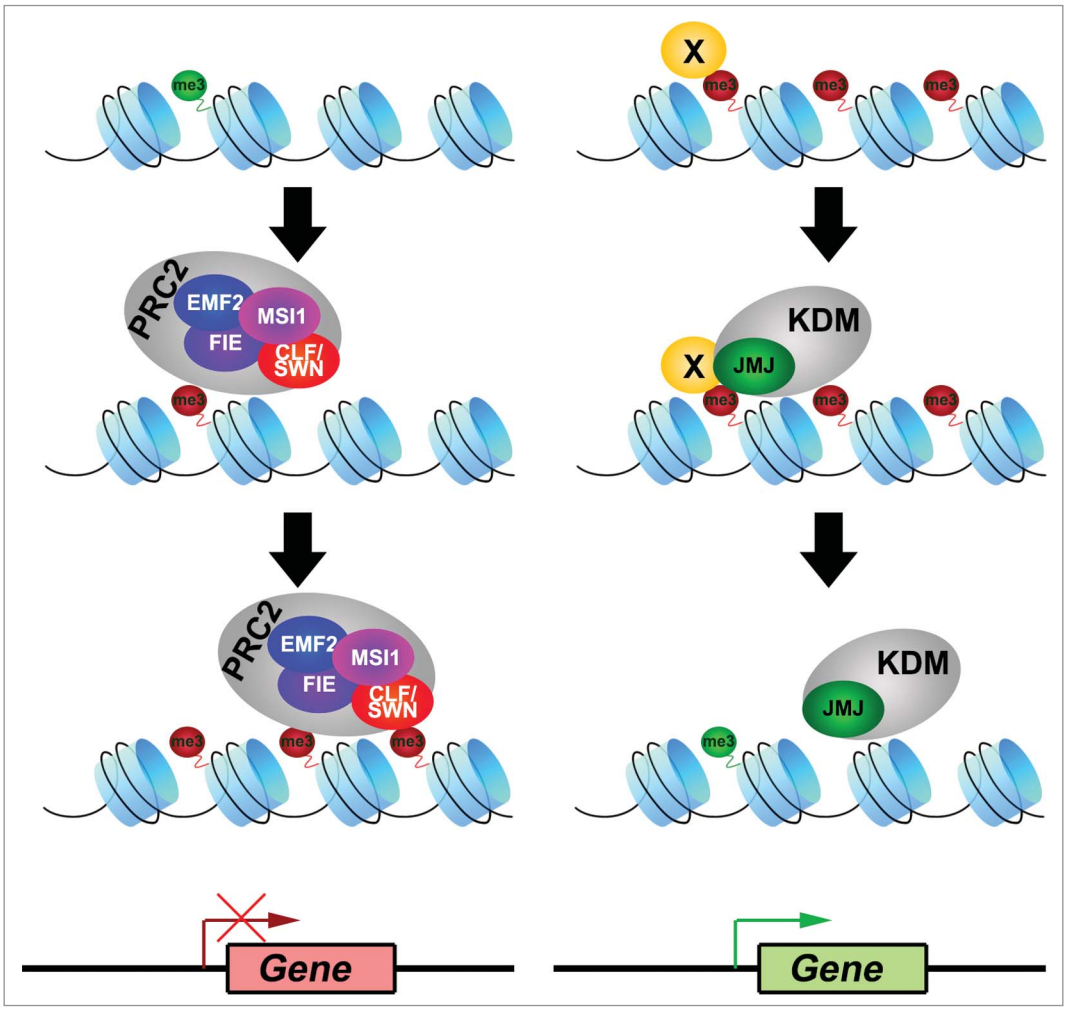

Figure 1. Antagonistic action of PRC2 and JMJ on gene regulation. Chromatin marked with active histone modification H3K4me3/H3K36me3 (green me3 circle) is in a permissive state of transcription. Recruitment of the Polycomb repressive complex 2 (PRC2) occurs possibly via the polycomb response elements (PREs). PRC2 complex containing core components of EMBRYONIC FLOWER 2 (EMF2), MULTICOPY SUPRESSOR OF IRA 1 (MSI1), FERTILIZATION INDEPENDENT ENDOSPERM (FIE), CURLY LEAF (CLF) or SWINGER (SWN) mediates the deposition and spreading of the repressive histone modification H3K27me3 (red me3 circle) across the region. This results in a repressive chromatin state and silences gene expression at the region. Functioning antagonistically, histone lysine demethylase (KDM) complex containing JUMONJI (JMJ) proteins, such as EARLY FLOWERING 6 (ELF6), RELATIVE OF EARLY FLOWERING 6 (REF6), JMJ30 or JMJ32, is recruited by unknown factors (factor X) to its target sites. The catalytic JMJ demethylases remove the H3K27me3 marks from the region. Coupled with the deposition of activating histone modifications, genes at the region can resume active transcription. These antagonistic actions of PRC2 and JMJ regulate the expression of genes including, but not limited to, the flowering regulators *FLOWERING LOCUS C* (*FLC*), *FLOWERING LOCUS T* (*FT*) and *SUPPRESSOR OF OVEREXPRESSION OF CO 1* (*SOC1*), to govern the flowering time of Arabidopsis.

PRC1 occupancy,[18] and vice versa PRC1-mediated H2A monoubiquitination can occur independent of PRC2 activity, as in *X*-inactivation mediated by *Xist* RNA.[19] Thus, it appears that gene repression may occur via the hierarchical or cooperative action of H3K27me3 and H2AK119ub marks or independently by either of the histone modifications.

The Arabidopsis genome contains homologs of all 4 core PRC2 components, and they are functionally conserved in which they mediate gene repression via the deposition of H3K27me3 marks on the chromatin (**Fig. 1**, reviewed in[2,20]). On the other hand, plants were once thought not to contain PRC1 complex due to the lack of some of the core PRC1 components, such as the H3K27me3-binding Pc protein. However, it was later shown that the homolog of the animal H3K9me2/3-binding Heterochromatin protein 1 (HP1) in Arabidopsis, LIKE HETEROCHROMATIN PROTEIN 1/TERMINAL FLOWER 2 (LHP1/TFL2) acts as the H3K27me3-binding protein and recruit putative the PRC1-like complex.[21] Furthermore, recent studies identified 5 PRC1 RING finger proteins in Arabidopsis: AtRING1A/B (homologs of Drosophila Sce) and AtBMI1A/B/C (homologs of Psc) (reviewed in[22,23]). TFL2, AtRING1A/B,[24] and AtBMI1A/B/C[25,26] interact to form a PRC1-like complex in Arabidopsis and catalyze the deposition of H2AK119ub.[25] Loss-of-function of *atring1a/b* and *atbmi1a/b* causes dedifferentiation of vegetative tissues into callus-like structures, which mimics the phenotype of *clf swn*[27] and *vrn2 emf2*[28] double mutants, indicating that *AtRING* and *AtBMI1* genes function in a similar pathway as PRC2 complex and are required to maintain the differentiated state of somatic cells.

It is noteworthy that a recent study showed that the triple mutant of the PRC1 components *atbmi1a/b/c* shows dramatic decrease of H3K27me3 on seed maturation genes, whereas the double mutant of the PRC2 components *clf swn* increased H2AK119ub, highlighting the direct or indirect regulation of each other's activity.[29] Moreover, genome-wide H2AK119ub level was not significantly affected in the *clf swn* mutant, suggesting that PRC1 targeting can occur through pathways independent of PRC2 in plants.[29] The Drosophila non-canonical PRC1 complex, called the dRing-associated factors (dRAF) complex, comprises Sce (Arabidopsis homologs: AtRING1A/B), Psc (Arabidopsis homologs: AtBMI1A/B/C), and KDM2, but lacks 2 components of the canonical PRC1 complex, Pc and Ph. Interestingly, mutation of *Sce* or *Psc* significantly decreases H2AK119ub levels, whereas depletion of *Pc* or *Ph* yield no effect on global H2AK119ub levels.[30] Thus, it is suggested that, compared to the canonical PRC1 complex, the plant PRC1-like complex may more resemble the dRAF complex, and may be recruited to the chromatin independently of H3K27me3 marks to catalyze the H2AK119 monoubiquitination.[22]

KDM3/JHDM3/JMJD2 Group H3K27me3 Demethylases Regulate Flowering Time

The KDM4/JHDM3/JMJD2 group of Arabidopsis JMJ proteins contain 3 members: AT5G04240/JMJ11/EARLY FLOWERING 6 (ELF6), AT3G48430/JMJ12/RELATIVE OF EARLY FLOWERING 6 (REF6) and AT5G46910/JMJ13. *ELF6* and *REF6* were genetically identified to have opposite functions in flowering time regulation.[31] Although the HMTase of H3K27me3 in Arabidopsis has been reported for almost 2 decades, the discovery of its demethylase has not been as successful. This is mainly because the metazoan H3K27me3 demethylases, Ubiquitously transcribed tetratricopeptide repeat X (UTX) and JMJD3,[32] do not have a homolog in plants. It is only recently that *ELF6*[33] and *REF6*[34] are reported as the H3K27me3 demethylase in Arabidopsis.

REF6 is the first plant H3K27me2/3 demethylase reported.[34] *REF6* is originally shown to function as a repressor of *FLOWERING LOCUS C* (*FLC*), the expression of which is increased in the *ref6* mutant.[31,35] However, overexpression of *REF6* causes drastic decrease of global H3K27me2/3 levels and produces phenotypes which resemble PRC2 mutants (i.e. early-flowering, curled leaf, embryonic flowering, etc).[34] The early-flowering phenotype is attributed to an *FLC*-independent up-regulation of the floral integrator *FLOWERING LOCUS T* (*FT*) and *SUPPRESSOR OF OVEREXPRESSION OF CO 1* (*SOC1*).[31,34] Moreover, the REF6 protein decreased H3K27me2/3 levels both *in vitro* and *in vivo*, and *ref6* mutant showed H3K27me3 hypermethylation in several hundred endogenous genes, confirming its role as an H3K27 demethylase.[34] Although REF6 contains C2H2 zinc finger domains at its C-terminal as a putative DNA-binding domain, it likely function as a complex like the metazoan UTX,[36] and requires other transcription factors to be recruited to its target genes. Recently, it is shown that the nuclear factor Y (NF-Y) complex interacts and recruits REF6 to the *SOC1* locus to remove the repressive H3K27me3 marks, thus promoting *SOC1* expression.[37]

ELF6 was initially screened to repress the floral integrators in the photoperiod pathway, whereby mutation of *elf6* results in increased *FT* and *SOC1* expressions and an early-flowering phenotype.[31] It is later reported that *ELF6* also participates in the reprogramming of the epigenetic state of the floral repressor *FLC*.[33] *FLC* is epigenetically silenced during vernalization (prolonged exposure to cold) to promote flowering upon returning to a warm condition,[38,39] and is reactivated during reproduction to ensure proper floral behavior in the next generation.[40] A hypomorphic mutant allele of *elf6–5* causes defect in the epigenetic resetting of *FLC* in which the H3K27me3 level at the locus is maintained at a higher level in the next generation when the parental plant is vernalized.[33] Furthermore, *ELF6* is shown to possess H3K27me2/3 demethylation activity *in vivo*.[33]

The KDM3/JHDM3/JMJD2 group contains one more member, JMJ13, which has no functional report thus far. The JMJ13 protein contains all conserved cofactor-binding amino acids, suggesting that it is enzymatically active.[12] However, its potential histone demethylation capability remains to be elucidated.

JmjC Domain-Only Group Contribute to Circadian and Thermosensory Regulations

The JmjC domain-only group of Arabidopsis JMJ proteins consists of 3 members, AT3G20810/JMJ30, AT5G19840/JMJ31, AT3G45880/JMJ32. Although AT5G63080/JMJ20 also does not have other recognizable protein domains besides a JmjC domain, its JmjC domain sequence is more similar to members of the JMJD6 group (AT5G06550/JMJ22 and AT1G78280/JMJ21). Furthermore, *JMJ20* and *JMJ22* are reported to function redundantly in controlling seed germination and catalyze histone arginine demethylation.[41]

Of the 3, *JMJ30* has been previously described as functioning in the circadian systems.[42,43] In the central circadian clock loop, TIMING OF CAB1 EXPRESSION 1 (TOC1) promotes the expression of morning-phased clock genes *CIRCADIAN CLOCK ASSOCIATED 1* (*CCA1*) and *LATE ELONGATED HYPOCOTYL* (*LHY*); CCA1 and LHY in turn repress *TOC1* in the evening, completing the feedback loop.[44] Functioning in a similar manner as TOC1 in the central clock loop, JMJ30 acts in concert with TOC1 to promote *CCA1* and *LHY* expression;[43] subsequently, CCA1 and LHY directly bind *JMJ30* and repress its expression.[42] Moreover, the *jmj30* mutant has shorter circadian period,[42,43] and decreased *CCA1* and *LHY* expression,[43] asserting its role in circadian regulation.

We recently showed that JMJ30 and its homolog JMJ32 contribute to the thermosensory pathway of flowering control by delaying the H3K27me3-mediated repression of *FLC* at higher temperatures.[45] Double mutant of *jmj30 jmj32* produces an early-flowering phenotype when grown at elevated temperatures. Conversely, overexpression of *JMJ30* results in a *FLC*-dependent late-flowering phenotype, with reduced H3K27me3 levels at the *FLC* locus, increased *FLC* mRNA expression and reduced *FT* and *SOC1* expressions.[42,45] Furthermore, JMJ30 is able to remove H3K27me3 *in vitro* and *in vivo*, affirming its role as an H3K27 demethylase. Although *JMJ30* is diurnally expressed, the JMJ30 protein is stabilized at higher temperature which leads to its increased accumulation. JMJ30 directly binds to the *FLC* locus, and its heat-stabilized activity likely maintain a permissive chromatin state at the locus.[45] The JMJ30/JMJ32-mediated *FLC* derepression thus constitutes a parallel mechanism in regulating floral transition with the other thermosensory pathways.[46]

This JMJ group contains another member, JMJ31, which may have lost its demethylase activity, since it has a different variant in one of its conserved key α-ketoglutarate (α-KG) binding residues.[12,47] Intriguingly, the first JMJ protein isolated in mouse, Jarid2/Jumonji, also has the same amino acid substitution.[48] The mouse Jarid2/Jumonji protein regulates multiple developmental processes including cardiac, haematopoietic and hepatic development.[49] Despite being enzymatically inactive, Jarid2/Jumonji interacts with other histone modifier to transcriptionally regulate its target genes.[49,50] Hence, it would be interesting to study the potential function of JMJ31 in modulating chromatin status of genes in Arabidopsis.

Substrate Specificity of JMJ Protein

More than a quarter of the Arabidopsis genes are targeted by H3K27me3. However, the fact that the phenotypes of *elf6, ref6, jmj30, jmj32* single mutants, *elf6 ref6, jmj30 jmj32* double mutants and *ref6 jmj30 jmj32* triple mutant are weaker than those of the metazoan H3K27 demethylase mutant hints that there might be more H3K27me3 demethylases waiting to be uncovered, or simply because plants have greater developmental plasticity or have more robust and flexible histone modification feedback.[45,51] Thus it might be interesting to observe the phenotype of the quadruple mutant of all currently known H3K27me3 demethylases, *elf6 ref6 jmj30 jmj32*, or a quintuple mutant of all potentially functional members of the KDM3/JHDM3/JMJD2 group and JmjC domain-only group, *elf6 ref6 jmj13 jmj30 jmj32*.

JMJ proteins from the same group are implicated to target similar histone modifications.[12,47] Despite residing in a different group with considerable diversifications in terms of domain architecture and JmjC domain sequence, members from the KDM3/JHDM3/JMJD2 group and JmjC domain-only group both target H3K27me3 marks. Such phenomenon is also observed in the mammalian genome as members from both the KDM2/JHDM1 group and KDM3/JHDM3/JMJD2 group are capable of H3K36 demethylation.[52] Crystal structures of REF6, ELF6, JMJ30, and JMJ32, with their cognate substrate (H3K27me3), will be helpful to determine their substrate specificity-determining amino acid residues.

Interestingly, the animal KDM3/JHDM3/JMJD2 group members target methylated H3K9 and H3K36,[47] and other previous studies on *ELF6* and *REF6* also reported similar substrate preferences.[35,51] One study shows that *ELF6* and *REF6* participate in the brassinosteroid (BR) signaling cascade through the transcription factor BRI1-EMS-SUPPRESSOR 1 (BES1).[51] BES1 recruits ELF6 and REF6 to the BR target genes (e.g. *TOUCH4* (*TCH4*)) and remove the H3K9 methylation to increase its expression, and thus BR-responsive phenotypes such as reduced cell elongation was observed in *elf6* and *ref6* mutants.[51] Another study reports that recombinant chimeric REF6–6×His is able to demethylate H3K4me2/3 and H3K36me2/3.[35] Moreover, REF6 can directly bind to the *FLC* locus and remove the activating histone modifications H3K4 and H3K36 methylation.[35] In addition, *FLC* expression is strongly up-regulated, rather than down-regulated, in the *ref6* mutant,[31,34,35] indicating that this increased *FLC* expression may be the main cause of the late-flowering phenotype in *ref6* mutant. This is supported by the observation that crossing of *ref6 flc* double mutant rescued the *ref6* late-flowering phenotype to a wild-type level.[31] Similar to *REF6, JMJ30* is also recently reported to be able to demethylate H3K36me2/3 *in vitro*.[53] A MYB transcription factor EARLY FLOWERING MYB PROTEIN (EFM) recruits JMJ30 to the *FT* locus and increases H3K36me2 levels at the region.[53]

The conflicting results among these reports suggest that JMJ proteins might have context dependent substrate specificity. Indeed, the metazoan JHDM3/JMJD2 group proteins such as JMJD2A show dual substrate specificities for 2 antagonizing H3K9 and H3K36 methylation marks, a repressive and

Table 1. *Arabidopsis* JMJ histone demethylases and their substrate specificity.

Group	Name	Locus	Substrate[a]	Methods[b]	Reference
KDM5/JARID1	JMJ15/MEE27	AT2G34880	H3K4me1/2/3	IV	6
	JMJ18	AT1G30810	H3K4me2/3	Ch, IT, HI	64
	JMJ14	AT4G20400	H3K4me1/2/3	Ch, IT, IV	65–67
	JMJ16	AT1G08620	NR	—	—
	JMJ19	AT2G38950	NR	—	—
	JMJ17	AT1G63490	NR	—	—
KDM4/JHDM3/JMJD2	JMJ12/REF6	AT3G48430	H3K9me3	Ch	51
			H3K4me2/3H3K36me2/3	Ch, IT	35
			H3K27me2/3	Ch, IT, IV, HI	34
	JMJ11/ELF6	AT5G04240	H3K9me3	Ch	51
			H3K27me2/3	Ch, IT, IV	33
	JMJ13	AT5G46910	NR	—	—
KDM3/JHDM2	JMJ26	AT1G11950	NR	—	—
	JMJ29	AT1G62310	NR	—	—
	JMJ25/IBM1	AT3G07610	H3K9me1/2	Ch, IV	68
	JMJ27	AT4G00990	NR	—	—
	JMJ24	AT1G09060	NR	—	—
	JMJ28	AT4G21430	NR	—	—
JMJD6	JMJ22	AT5G06550	H3R2me2H4R3me1/2s	Ch	41
	JMJ21	AT1G78280	NR	—	—
	JMJ20	AT5G63080	H3R2me2H4R3me1/2s	Ch, IT	41
JmjC domain-only	JMJ30	AT3G20810	H3K27me2/3	Ch, IT, IV	45
			H3K36me2/3	Ch, IT	53
	JMJ31	AT5G19840	NR	—	—
	JMJ32	AT3G45880	H3K27me3	Ch, IV	45

[[a]NR, No report].
[[b]Ch, chromatin immunoprecipitation (ChIP); IT, *in vitro* demethylation assay; IV, *in vivo* demethylaion assay; HI, total histone immunoblot].

activating mark respectively.[47] These differences may also be due to indirect effects of histone modification crosstalks, as activating and repressing histone marks frequently show opposing dynamics.[54,55] Furthermore, other JMJ proteins may retain minimal degree of substrate-flexibility and undertake non-endogenous function to compensate an extreme situation where one type of histone demethylation is compromised, as seen in the compensatory mechanism in DNA methylation.[56] Similar compensatory mechanisms are evident in transcription factor activity. The carpel and fruit development gene *FRUITFULL* (*FUL*) can compensate the loss of the 2 floral meristem identity genes *apetala1* (*ap1*) and *cauliflower* (*cal*) to mediate flower initiation, such that triple mutant of *ful ap1 cal* causes an even more severe phenotype than *ap1 cal* and produces leafy shoots in place of flowers.[57] Similarly, the carpel-/fruit-specific MADS-box genes *SHATTERPROOF1* (*SHP1*) and *SHP2* also assume a non-endogenous role of *AGAMOUS* (*AG*)-compensatory activity in carpel formation in the *apetala2* (*ap2*) *ag* double mutant.[58] These partial compensations may be evolutionary remnants of the MADS-box and JMJ genes which retain some functional plasticity.

Conclusions and Perspectives

Post-translational histone modifications at their N-terminal tails regulate chromatin activity in distinct biological settings. Having common histone modifications such as H3K27me3 will allow group of genes functioning in the same developmental process to be regulated in a similar manner, e.g., seed maturation genes are repressed during vegetative growth and only activated during seed development.[59,60] Moreover, H3K27 methylation acting in concert with other histone modifications will produce new 'histone code', such as the poised chromatin state of bivalent H3K27me3 and H3K4me3 marks.[61,62] Although methylated histone marks may be diluted with cell cycle progression,[63] having active histone demethylase such as JMJ and LSD1 proteins will allow faster response to endogenous and environmental cues.

We are beginning to understand the enzymatic activity of JMJ proteins, yet we still do not fully understand their biological roles. Many Arabidopsis genes are targeted by histone modifications but *jmj* mutants mostly produce flowering phenotypes.[31,45,64-67] Although hundreds of genes are mis-regulated in the *jmj* mutants, only few of the target genes are studied in detail. Thus, genome wide ChIP-seq of JMJ proteins coupled with the expression data will aid in identifying their direct targets. Moreover, the mechanism of recruitment of these histone modifiers to specific target is of interest. A screen of JMJ-interacting partners may identify their recruiting transcription factors and also potentially uncover their roles in a larger complex. Further genetic, biochemical, and molecular analysis would increase our understanding of the functions and mechanisms of histone methylation in epigenetic regulation.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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